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BRIEF COMMUNICATION

Altitude and arteriolar hyalinosis after kidney transplantation

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Abstract

The kidney is very susceptible to hypoxic injury. Calcineurin inhibitors (CNIs) induce vasoconstriction and might reduce renal tissue oxygenation. We aimed to investigate if the synergistic deleterious effects of CNI-treatment and hypoxia of high altitude living might accelerate the development of arteriolar hyalinosis in kidney allografts. We stratified all patients who received a kidney graft from 2000 to 2010 in our center (N=477) in 3 groups according to the residential elevation (below 400, between 400 to 600 and above 600 m above sea level) and we retrospectively re-evaluated all transplant biopsies performed during follow-up specifically looking at the degree of arteriolar hyalinosis, the hallmark of chronic CNI nephrotoxicity. Living at high altitude was markedly associated with a higher degree of arteriolar hyalinosis ($p<0.001$). Hemoglobin levels confirmed the functional relevance of different arterial oxygenation among the groups ($p=0.01$). Thus, patients living at high altitude seem to be more susceptible to the developemt of arteriolar hyalinosis after kidney transplantation.

Key words: altitude, hypoxia, cyclosporine, tacrolimus, transplantation.

Introduction

The immunosuppressive potency of calcineurin inhibitors (CNIs) revolutionized transplantation medicine in the 1980s, their nephrotoxic effects however negatively impact long-term graft survival after kidney transplantation (1, 2). The pathophysiological processes determining chronic CNI nephrotoxicity are not well elucidated and it has been difficult to reproduce this complex clinical picture in animal models (3). A combination of direct toxic effects and hemodynamic changes leads to tubulo-interstitial, glomerular and vascular damages. Importantly, CNIs induce vasoconstriction of the afferent arterioles, which exacerbate renal hypoxia (4). The renal tissue is marginally oxygenated also under physiological conditions and several molecular mechanisms are involved in the adaptation to changes in renal oxygenation, but the kidney remains very susceptible to hypoxic injury (5). As a clinical correlate, people living at high altitude under chronic hypoxic conditions often present signs of renal damage (a novel clinical entity recently defined as *High Altitude Renal Syndrome* - HARS) (6), and an accelerated progression of chronic kidney disease particularly in diabetic nephropathy (7, 8). In our daily clinical practice we observed a high prevalence of chronic CNI toxicity in kidney transplant recipients living in mountainous regions. We hypothesized that arterial hypoxia and CNIs might synergistically contribute to renal damage after kidney transplantation. A systematic analysis of transplant biopsies performed in patients living at different altitudes was used to investigate this hypothesis.

Methods

All adult patients who received a kidney transplant from a deceased donor at the University Hospital Zurich between 2000 and 2010 and who had a transplant biopsy beyond the first month after transplantation were considered. Patients are referred to our center for transplantation from different parts of Switzerland, including regions located in the Swiss

Alps. Standardized immunosuppression is guided homogeneously through a close collaboration with the referral centers and yearly appointments in Zurich. All kidney biopsies were performed because of a clinical indication.

We retrospectively assessed the histopathological evaluation of all biopsies performed during follow-up. The biopsies were analyzed by different pathologists according to Banff criteria (for arteriolar hyalinosis ah grade 0 to 3) (9). The degree of arteriolar hyalinosis, the hallmark of chronic CNI nephrotoxicity (10), was correlated with the residential altitude. Patients were stratified in 3 groups according to the altitude they were living. The definition of altitude ranges for patient stratification was chosen arbitrarily to obtain 3 groups with at least 15 patients in each group. To assess the development of arteriolar hyalinosis over time we defined 3 periods of interest. Biopsies performed in the first 90 days after transplantation primarily reflect the quality of the graft at time point of transplantation and were excluded to avoid confounders related to graft allocation or the early clinical course after transplantation. In consideration of previous reports (1), we expected a high degree of arteriolar hyalinosis in most biopsies taken beyond 2000 days after transplantation. The period of interest to evaluate an association between residential elevation and the development of arteriolar hyalinosis was therefore between 90 and 2000 days after transplantation. We compared means and proportions using Kruskal-Wallis and Chi-square test, respectively. The study was approved by the local ethics committee.

Results

Among the 477 patients considered for this study, in 184 cases at least one biopsy was performed beyond the first month after transplantation. The patients were stratified in 3 groups: 38 patients lived below 400 m above sea level (77 biopsies), 129 patients between 400 and 600 m (297 biopsies) and 17 patients above 600 m (35 biopsies). Among the groups

there were no differences in the baseline characteristics, including age, sex, primary kidney disease and cold ischemia time (Table 1).

The degree of arteriolar hyalinosis in biopsies performed in the first 90 days after transplantation did not differ among residential elevation groups, thereby excluding differences related to the baseline characteristics of the grafts or the early clinical course after transplantation. In contrast, we found a strong association between the residential elevation and the degree of arteriolar hyalinosis starting at day 90 after transplantation (Figure, $P<0.001$). Similar results were obtained by considering only the first biopsy performed beyond day 90 after transplantation ($P=0.004$), thereby excluding a bias related to multiple biopsies from the same patient. Other parameters with a possible impact on CNI-toxicity and arteriolar hyalinosis including blood pressure, drug levels and smoking did not differ among the groups at the time point of the first biopsy beyond day 90 after transplantation. Importantly, higher hemoglobin levels in patients living at higher altitude confirmed that the difference in atmospheric pO_2 was functionally relevant (Table 2). Patients with severe arteriolar hyalinosis (ah grade 2 or 3) lived at higher altitude ($P<0.001$), had higher creatinine levels ($P=0.01$) and presented a higher degree of interstitial fibrosis and tubular atrophy, a less specific feature of CNI nephrotoxicity ($P=0.003$). Finally, the development of arteriolar hyalinosis was strongly associate with time ($P<0.001$), and in biopsies performed >2000 days after transplantation severe arteriolar hyalinosis was almost universally present (Figure, Panel A).

Discussion

Living at higher altitude was associated with an accelerated development of high-grade arteriolar hyalinosis. The unique characteristics of our cohort, including patients living at different altitudes treated with a standardized immunosuppressive protocol, revealed this previously unknown but physiologically plausible association. The stepwise increase in arteriolar hyalinosis related to the altitude levels and the solid statistical evidence despite a relatively small number of patients emphasize the relevance of this finding. Interestingly, a large proportion of subjects living >600 m had a very high degree of arteriolar hyalinosis despite lower CNI levels and the absence of smokers in this group. The study design does not allow any conclusion about causality, but the data suggest a link between a minimal but functionally relevant reduction in atmospheric pO_2 and the development of arteriolar hyalinosis. The assumption of a direct synergistic effect of CNI and tissue hypoxia on the metabolically challenged single organ transplant is tempting, but other indirect or CNI-independent mechanisms cannot be excluded. From a clinical perspective, these novel and somehow surprising findings highlight the need to consider environmental factors contributing to changes seen in kidney morphology.

Disclosure

The authors declare no competing financial interest.

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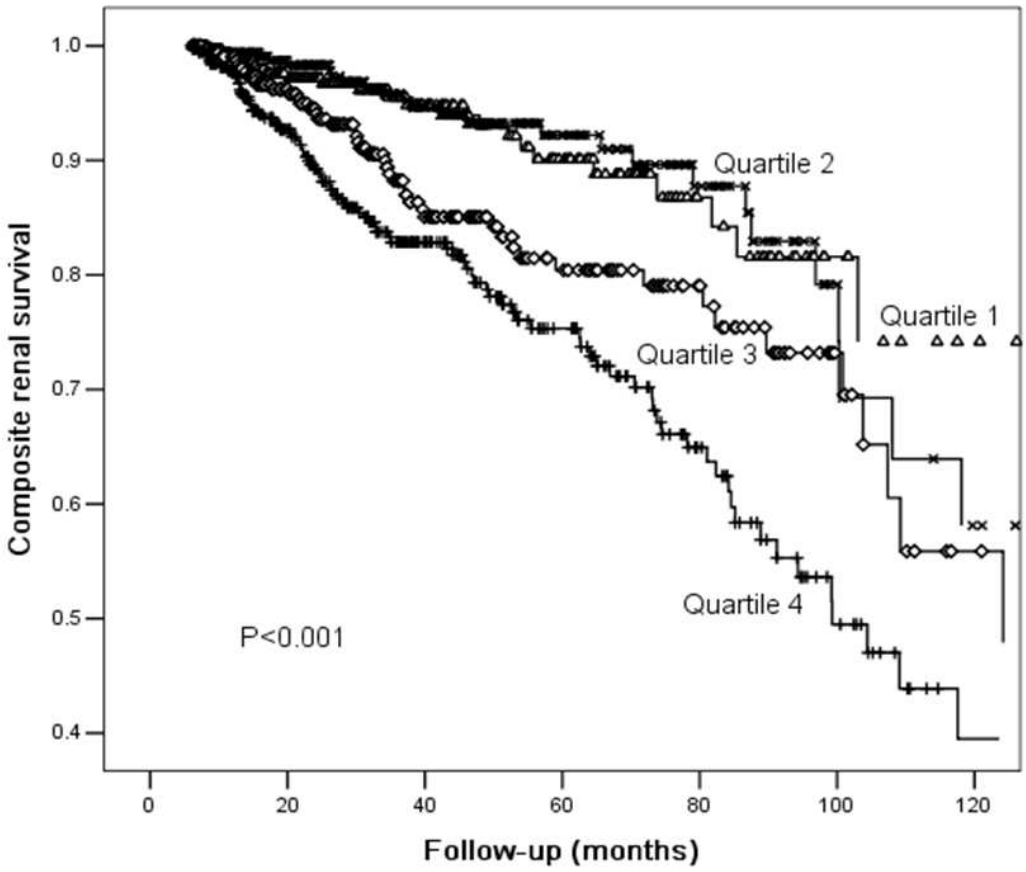

Quartile 1	339	127	34	6
Quartile 2	360	152	46	9
Quartile 3	338	129	45	8
Quartile 4	393	160	53	9

Panel A: Grade of arteriolar hyalinosis according to Banff classification (ah 0-3) in all biopsies in relation to the time point of biopsy and stratified by the patient's living altitude.

Panel B: Grade of arteriolar hyalinosis in biopsies performed between day 90 and 2000 stratified by residential elevation.

Table 1. Baseline characteristics of the transplant patients living at different altitudes

	Residential Elevation, m			
	<400 (N=38)	*400-600 (N=129)*	*>600 (N=17)*	*P*
Living altitude – meters above sea level[#]	306 ± 70	444 ± 48	1101 ± 425	<0.001 *
Age at transplantation – year	49 ± 13	52 ± 13	53 ± 14	0.19
Male sex – no. (%)	27 (71)	88 (68)	8 (47)	0.18
Primary kidney disease – no. (%)				0.62
- Diabetic nephropathy	4 (11)	12 (9)	1 (6)	
- Hypertensive nephropathy	1 (3)	11 (9)	3 (18)	
- Glomerulonephritis	17 (45)	44 (34)	5 (29)	
- Urological disease	3 (8)	6 (5)	0 (0)	
- Polycystic kidney disease	4 (11)	20 (16)	4 (24)	
- Unknown	4 (11)	24 (19)	1 (6)	
- Other	5 (13)	12 (9)	3 (18)	
Cold ischemia time – minutes	749 ± 310	758 ± 290	759 ± 294	0.93

[#] Standard barometric pressure at 306, 444 and 1101 m: 98 kPa, 96 kPa, 89 kPa, respectively. Atmospheric partial pressure of oxygen (pO_2): 20.6 kPa, 20.2 kPa, 18.7 kPa, respectively. Available oxygen compared to see level: 97%, 95% and 88%, respectively.

* Statistically significant, $P<0.05$.

Table 2. Characteristics at time point of the first biopsy performed beyond day 90 after transplantation

	Residential Elevation, m			
	<400 (N=34)	*400-600 (N=101)*	*>600 (N=10)*	*P*
Time – day after transplantation	580 ± 537	611 ± 535	607 ± 497	0.81
Systolic blood pressure – mmHg	141 ± 20	137 ± 18	141 ± 14	0.56
Diastolic blood pressure – mmHg	80 ± 13	80 ± 13	82 ± 11	0.67
Smoker – no. (%)	4 (12)	19 (18)	0 (0)	0.23
Antihypertensive drugs – no.	2.3 ± 1.4	2.7 ± 1.3	2.2 ± 1.0	0.10
ACE inhibitor or angiotensin receptor blocker – no. (%)	18 (52)	54 (53)	4 (40)	0.72
Calcium channel blocker – no. (%)	13 (38)	51 (50)	4 (40)	0.42
Creatinine – µmol/l	208 ± 118	191 ± 84	210 ± 85	0.67
CNI (Ciclosporine A / Tacrolimus) – no.	20 / 14	56 / 45	2 / 8	0.08
Cyclosporine A – C0 level in µg/l	144 ± 65	135 ± 56	102 ± 72	0.59
Tacrolimus – C0 level in µg/l	8.9 ± 3.7	8.6 ± 3.3	8.4 ± 1.8	0.94
Hemoglobin – g/l	106 ± 16	117 ± 18	118 ± 15	0.01*
Mean IFTA – %	21 ± 24	15 ± 14	13 ± 10	0.48

Abbreviations: CNI, calcineurin inhibitor; C0, drug trough level; IFTA, interstitial fibrosis and tubular atrophy.

* Statistically significant, $P<0.05$.